U.S. HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

JUSTIFICATION, TEST PLAN, AND ROBUST SUMMARIES

PHOSPHITE ISODECYL/PHENYL CHEMICAL CATEGORY:

Phosphorous acid, triisodecyl ester (CAS# 25448-25-3)

Phosphorous acid, diisodecyl phenyl ester (CAS# 25550-98-5)

Phosphorous acid, isodecyl diphenyl ester (CAS# 26544-23-0)

Phosphorous acid, triphenyl ester (CAS# 101-02-0)

Prepared by:

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on behalf of the
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September 10, 2001

Prepared for:

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Introduction

Under the High Production Volume (HPV) Challenge program, the United States EPA has provided for the grouping of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity. Grouping related chemicals into categories has several benefits reducing the number of animals needed for testing, reducing cost the overall testing program, and man accelerate the dissemination of hazard information to the public.

Chemical categories may be based on:

- A common functional group
- An incremental and constant change across the category **OR**
- The likelihood of common precursors and/or breakdown products, via either physical or biological processes, which result in structurally similar chemicals

The Phosphite Producers HPV Consortium (PPHC) and the Phosphite Manufacturers Consortium (PMC) propose to group four phosphite stabilizers into a category for the purposes of testing under the U.S. HPV Challenge. The proposed category will consist of:

- Phosphorous acid, triphenyl ester (CAS# 101-02-0), also known as triphenyl phosphite (TPPi)
- Phosphorous acid, isodecyl diphenyl ester (CAS# 26544-23-0), also known as isodecyldiphenyl phosphite (DPDP)
- Phosphorous acid, diisodecyl phenyl ester (CAS# 25550-98-5), also known as diisodecylphenyl phosphite (PDDP)
- Phosphorous acid, triisodecyl ester (CAS# 25448-25-3), also known as triisodecyl phosphite (TDP)

The category is based on the common functional group (phosphite ester), the successive change across the series of aryl to alkyl ester, and the similarity in manufacturing process and expected breakdown/hydrolysis products. By grouping these chemicals into a category, overall testing will be reduced as outlined below:

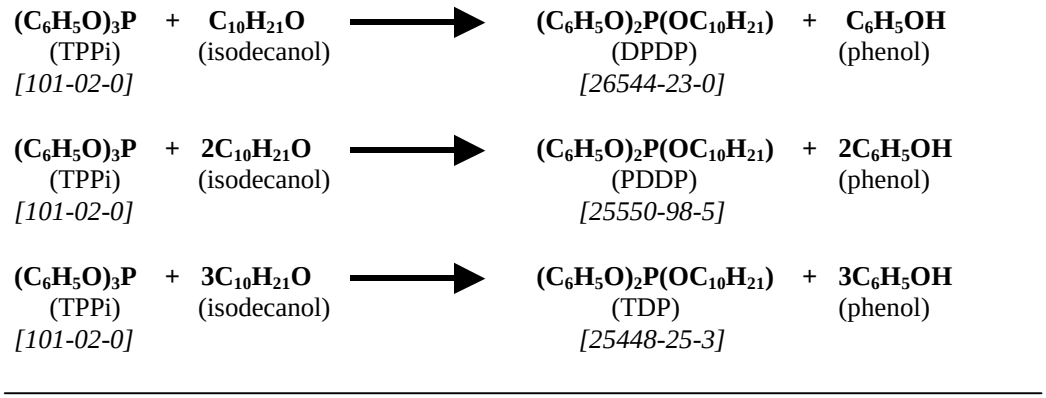
- Combined repeat dose, reproductive and developmental toxicity - 2 of 4 compounds will be tested
- Acute toxicity to fish, algae, and *Daphnia* - 2 of 4 compounds will be tested (combined with existing data on 2 compounds)
- *In vitro* Mammalian cell mutation assay - 2 of 4 compounds will be tested
- Biodegradation - 2 of 4 compounds will be tested (combined with existing data on 1 compound)

Manufacturing and Use Information

Manufacturing/Composition

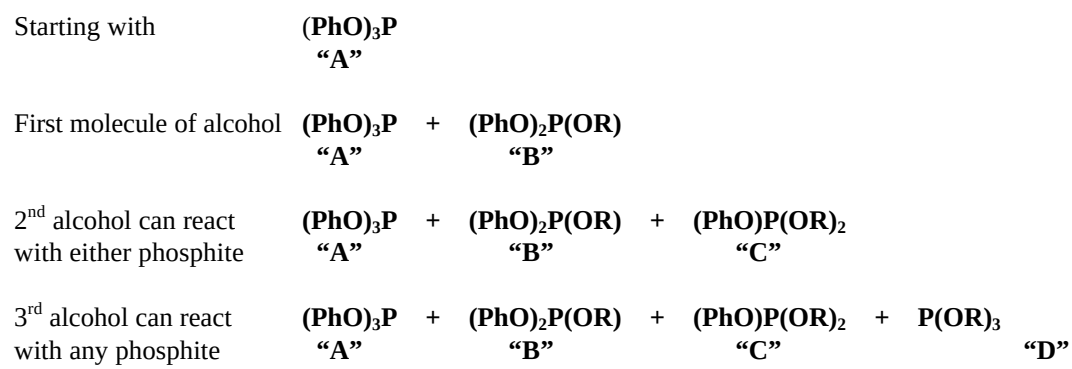
The proposed category consists of phosphorous acid, triphenyl ester, as well as three products manufactured from triphenyl phosphite. In sequence from phosphorous acid, isodecyl diphenyl ester to phosphorous acid, diisodecyl phenyl ester, and finally phosphorous acid, triisodecyl ester, the products are manufactured by reacting different mole ratios of isodecyl alcohol with triphenyl phosphite, liberating phenol. The specific reactions are shown in Figure 1.

Figure 1: Manufacture



Transesterification reactions as described in Figure 1, however, are not specific. An outline of the possible reactions is shown in Figure 2.

Figure 2: Distribution of Transesterification Products



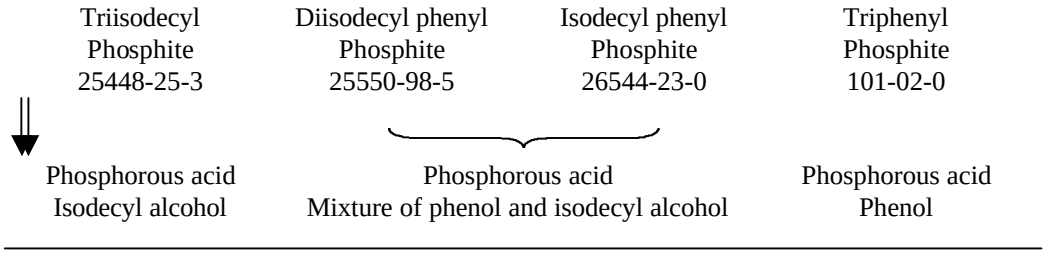
Transesterification of phenol with isodecanol to give triisodecyl phosphite from triphenyl phosphite (i.e., "A" to "D") proceeds cleanly. Commercial triphenyl phosphite and triisodecyl phosphite are 98+% pure. However, for the partially transesterified products diphenylisodecyl phosphite and phenyldiisodecyl phosphite, the reaction product obtained is actually a mixture

of “A”, “B”, “C”, and “D” as shown in Figure 2. The ratio of each is controlled by the mole ratio of triphenyl phosphite and isodecanol reacted, and various other manufacturing conditions. It is not practical to produce pure diphenylisodecyl phosphite and phenyldiisodecyl phosphite. Diphenylisodecyl phosphite and phenyldiisodecyl phosphite sold in commerce typically range from 50-70% pure.

Degradation

The most common form of degradation for phosphites is hydrolysis. Each of the phosphites in this category will hydrolyze to phosphorous acid and either phenol or isodecanol, or a mixture of both, depending on the amount of transesterification from aryl to alkyl phosphite. The expected hydrolysis products are shown in Figure 3.

Figure 3: Hydrolysis Products



Use

These products are secondary antioxidants used in polymer manufacture to improve color, processing, heat, and UV stability. These liquid phosphites are normally added to the polymer at 0.25-1.0% by weight to achieve the desired protection. Polymers that use these products include polyolefins, ABS, synthetic rubber, PVC, epoxies, polyurethanes, polyesters, and adhesives. Applications of polymers using these products are numerous. Diphenylisodecyl phosphite and phenyldiisodecyl phosphite are used primarily in non-food contact PVC applications as well as in polyurethanes. Triisodecyl phosphite is useful in many polymers and in lubricants where food-contact approval is not required. In addition to being a generally useful antioxidant for many polymers, triphenyl phosphite is also used in epoxy resin systems as a reactive diluent. The epoxy system is useful in such applications as adhesive coatings, laminates, potting and soldering compounds, and tooling.

Development of the Category

EPA has provided guidance on developing and justifying chemical categories:

- Develop a potential category by grouping a series of like chemicals.
- Gather published and unpublished literature on physicochemical characteristics and health and environmental effects.
- Evaluate the available data for adequacy.
- Construct a matrix of SIDS endpoints vs. category members arranged in order of the structural progression of the category.
- Evaluate the endpoints to determine whether data correlate with the structure.

- Make the category rationale and testing scheme available for review.
- Perform the testing.
- Add new data to the matrix and confirm that the data support the category rationale.

Category Definition

As mentioned above, EPA has provided for the grouping of chemicals whose physicochemical and toxicological properties are likely to be similar or to follow a regular or predictable pattern. The category may be based on a common functional group, an incremental and constant change across the category, or common precursors and/or breakdown products. Data is extrapolated or interpolated to assess chemicals in the category rather than conducting additional testing on individual category members. If there is not sufficient existing information, the test plan for the category should include obtaining sufficient data to support the category.

We have already shown that the chemicals in this organophosphite category are manufactured from the same materials. Due to the manufacturing process itself, each of the chemicals in this category may be present as impurities and/or byproducts in the individual products, particularly in the case of diphenylisodecyl phosphite and phenyldiisodecyl phosphite. Therefore these materials are linked by the common organophosphite functionality and by the common breakdown products (Figure 3). The category is also defined by the change of alkyl vs. aryl ester ratio as we move across the category and by the residual amount of triphenyl phosphite remaining in the product from the manufacturing process (Figure 4). It is postulated that differences in observed toxicity can be explained and predicted by these changes.

Figure 4: Incremental Changes

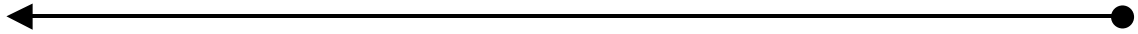
Product:	Triisodecyl Phosphite	Diisodecyl phenyl Phosphite	Isodecyl phenyl Phosphite	Triphenyl Phosphite
CAS RN	25448-25-3	25550-98-5	26544-23-0	101-02-0
Alkyl : Aryl ratio	3 : 0	2 : 1	1 : 2	0 : 3
% 101-02-0	0-2	0-5	20-30	100

Matrix of HPV Endpoints (Available Data)

To construct this matrix, existing data for all of the category chemicals were gathered and evaluated for adequacy. The results are shown in Tables 1-4.

Table 1. Summary of Physical and Chemical Data

Increasing Alkyl : Aryl ratio



Study Type	**Triisodecyl Phosphite (CAS# 25448-25-3)**	**Diisodecylphenyl Phosphite (CAS# 25550-98-5)**	**Isodecyldiphenyl Phosphite (CAS# 26544-23-0)**	**Triphenyl Phosphite (CAS# 101-02-0)**
PHYSICAL AND CHEMICAL DATA				
1.0 Melting Point	No Data	No Data	No Data	No Data
2.0 Boiling Point	No Data	No Data	No Data	No Data
3.0 Vapor Pressure	No Data	No Data	No Data	No Data
4.0 Partition Coefficient	No Data	No Data	No Data	No Data
5.0 Water Solubility	No Data	No Data	No Data	No Data

Increasing TPPi content

Table 2. Summary of Environmental Fate & Pathway/Ecotoxicity Data

Increasing Alkyl : Aryl ratio

STUDY TYPE	**Triisodecyl Phosphite (CAS# 25448-25-3)**	**Diisodecylphenyl Phosphite (CAS# 25550-98-5)**	**Isodecyldiphenyl Phosphite (CAS# 26544-23-0)**	**Triphenyl Phosphite (CAS# 101-02-0)**
ENVIRONMENTAL FATE & PATHWAY				
6.0 Photodegradation	No Data	No Data	No Data	No Data
7.0 Stability in Water	No Data	No Data	No Data	No Data
8.0 Transport and Distribution	No Data	No Data	No Data	No Data
9.0 Biodegradation	No Data	Not Readily Biodegradable	No Data	No Data
ECOTOXICITY				
10.0 Acute Toxicity to Fish (LC50: 96 Hour)	No Data	> 100 mg/L (48-hr) (max. soluble conc.)	> 16 mg/L (max. soluble conc.)	No Data
11.0 Acute Toxicity to Algae (EC50: 72 Hour)	No Data	45 mg/L	1.6 mg/L	No Data
12.0 Acute Toxicity to *Daphnia* (EC50: 48 Hour)	No Data	0.2 mg/L	1 to 5 mg/L	No Data

Increasing TPPi content

Table 3. Summary of Toxicology Data

Increasing Alkyl : Aryl ratio

STUDY TYPE	**Triisodecyl Phosphite (CAS# 25448-25-3)**	**Diisodecylphenyl Phosphite (CAS# 25550-98-5)**	**Isodecyldiphenyl Phosphite (CAS# 26544-23-0)**	**Triphenyl Phosphite (CAS# 101-02-0)**
TOXICOLOGY				
13.1 Acute Toxicity (Oral)	> 5 g/kg	> 5 g/kg	4 g/kg	1.6 g/kg
13.2 Acute Toxicity (Dermal)	> 5 g/kg	> 5 g/kg	> 5 g/kg	>2 g/kg but <5 g/kg
13.3 Acute Toxicity (Inhalation)	> 12.6 mg/L (max attainable conc.)	> 11.7 mg/L (max attainable conc.)	> 8.4 mg/L (max attainable conc.)	> 6.7 mg/L (max attainable conc.)
14.0 Genotoxicity *In Vitro or In Vivo* (Chromosome Aberration Tests)	Negative (Micronucleus Test)	Negative (Micronucleus Test)	Negative (Micronucleus Test)	Negative (Micronucleus Test)
15.1 Genotoxicity *In Vitro* (Bacterial Test)	Not mutagenic	Not mutagenic	Not mutagenic	Not mutagenic
15.2 Genotoxicity *In Vitro* (Mammalian Cells)	No Data	No Data	No Data	No Data
16.0 Repeated Dose Toxicity	No Data	No Data	No Data	No Data
17.0 Reproductive Toxicity	No Data	No Data	No Data	No Data
18.0 Developmental Toxicity/ Teratogenicity	No Data	No Data	No Data	No Data

Increasing TPPi content

Table 4. Summary of Other Non-HPV Toxicology Data for Consideration

Increasing Alkyl : Aryl ratio

STUDY TYPE	**Triisodecyl Phosphite (CAS# 25448-25-3)**	**Diisodecylphenyl Phosphite (CAS# 25550-98-5)**	**Isodecyldiphenyl Phosphite (CAS# 26544-23-0)**	**Triphenyl Phosphite (CAS# 101-02-0)**
TOXICOLOGY -OTHER (NON-HPV) ENDPOINTS				
Primary Eye Irritation	Slight Draize = 10.0/110)	Slight (Draize = 10.3/110)	Slight Draize = 9.3/110)	Slight (Draize = 10.3/110)
Primary Skin Irritation	Moderate (Draize = 5.4/8.0)	Moderate (Draize = 4.5/8.0)	Moderate (Draize = 4.6/8.0)	Moderate (Draize = 4.1/8.0)
Neurotoxicity	No Data	Weakly Neurotoxic in Hens	Weakly Neurotoxic in Hens	Highly Neurotoxic in Hens, Rats, and Beagle Dogs

Increasing TPPi content

Overview of Existing Test Results

Based on the information presented in Tables 2 and 3, there appears to be a clear progression of effects from less toxic to more toxic as the number of phenyl groups increase and concomitantly the number of isodecyl groups decreases; or alternately as the amount of triphenyl phosphite increases. For example, the acute aquatic toxicity values in fish and algae for the diisodecyl group (LC_{50} > 100 mg/L and EC_{50} = 45 mg/L, respectively) indicate a lower degree of toxicity compared to the monoisodecyl group (LC_{50} >16 mg/L and EC_{50} = 1.6 mg/L, respectively). The 48-hour EC50 values in *Daphnia* were comparable for these two materials (0.2 mg/L and 1-5 mg/L, respectively).

For mammalian toxicology end-points, the pattern of less toxic to more toxic is quite evident as the number of phenyl groups increases, or alternately as the triphenyl phosphite increases. The acute oral LD_{50} for both the tri- and diisodecyl materials is greater than 5 g/kg, whereas the monoisodecyl decreases to 4 g/kg and the pure triphenyl phosphite, the material without isodecyl groups, is the most toxic at 1.6 mg/kg. A similar progression is evident for the acute dermal LD_{50} as triphenyl phosphite is more toxic than the other compounds. Where all four materials respond similarly (e.g., *in vitro* bacterial tests and *in vivo* chromosome aberrations tests), the degree of toxicity is slight or totally absent (e.g., none of the four materials was genotoxic in either of the two test systems used).

Although not a concern of the US EPA program, the pattern holds for other non-HPV mammalian and non-mammalian toxicology tests as well (Table 4). There was only very slight neurotoxicity in the hen assay with the di- and monoisodecyl materials, but the material without any isodecyl groups, triphenyl phosphite, was highly neurotoxic, not only to hens, but also to rats and dogs.

Robust summaries are available for each of the four compounds and are attached to this document (Appendix).

Proposed Testing Strategy

Based on the available information, these four materials appear to meet all of the criteria to be considered as a category. The testing scheme for the four materials is presented in Table 5 and outlined here.

<u>Physical and Chemical Properties Data</u>
PMC proposes to develop data on each of the four products for the following physical chemical properties:

- Melting Point
- Boiling Point
- Vapor Pressure
- Octanol/Water Partition Coefficient
- Water Solubility

Environmental Fate and Effects

PMC proposes to develop data on each of the four products for the following:

- Photodegradation
- Stability in Water
- Transport and Distribution

With regards to biodegradation, since adequate data exist for one of the interior products (PDDP), PMC proposes to test only the outer members of the category (TDP and TPP).

Ecotoxicity

Since adequate data exists for the interior products (PDDP and DPDP), PMC proposes testing only the outer members of the category (TDP and TPP) for the following:

- Acute Toxicity to Fish
- Acute Toxicity to Algae
- Acute Toxicity to *Daphnia*

Mammalian Toxicity

Adequate data exists for the four members of the category for acute oral, dermal, and inhalation toxicity, as well as for the Ames mutagenicity and *in vivo* chromosomal aberration assays. There are no data available for reproductive, developmental, or repeated dose toxicity for any of the four materials. PMC proposes testing only the outer members of the category (TDP and TPPi) for the following:

- *In vitro* mammalian cell mutation assay
- Combined repeat dose, reproductive, and developmental toxicity

Test Plan Rationale

By testing the "outside members" of the category, the toxicity of the "interior members" can be inferred if the two materials on the ends have similar toxic responses. For example, if there is no toxicity noted in a test with the triisodecyl and the "zero" isodecyl material (TPPi), then the mono- and diisodecyl materials would not be expected to exhibit any toxic effects in the same test. If the two end materials are significantly different (i.e., one produces a severe toxic effect and the other produces no toxic effect), then testing will be conducted on one or both of the interior materials, depending on the nature of the effects observed and the magnitude of the observed differences.

Testing Schedule

Based on this testing plan, we are rearranging our commitment to EPA for the order of testing to permit triphenyl phosphite and triisodecyl phosphite to begin testing in 2001. Any subsequent testing required because of significant differences in toxic responses would be conducted during the following year. Triisodecyl phosphite is currently scheduled for initiation of testing in 2002 and triphenyl phosphite is currently scheduled for testing beginning in 2003. The mono- and diisodecyl phosphites are scheduled for

2001. We would, therefore, propose to begin the testing for the triphenyl and triisodecyl phosphites upon approval of the category by EPA and the necessary 120-day posting period on the EPA HPV website for external comments. This would move the start of testing, if needed, for the "interior" materials from 2001 to 2002.

Table 5. Proposed Test Plan for the Isodecyl/Phenyl Phosphite Category Members

Increasing Alkyl : Aryl ratio ←

Study Type	Triisodecyl Phosphite[1] (CAS# 25448-25-3)	Diisodecylphenyl Phosphite (CAS# 25550-98-5)	Isodecyldiphenyl Phosphite (CAS# 26544-23-0)	Triphenyl Phosphite (CAS# 101-02-0)
1.0 Melting Point	**TEST (OECD 102)**	**TEST**	**TEST**	**TEST**
2.0 Boiling Point	**TEST (OECD 103)**	**TEST**	**TEST**	**TEST**
3.0 Vapor Pressure	**TEST (Calculation)**	**TEST**	**TEST**	**TEST**
4.0 Partition Coefficient	**TEST (OECD 107)**	**TEST**	**TEST**	**TEST**
5.0 Water Solubility	**TEST (OECD 105**	**TEST**	**TEST**	**TEST**
6.0 Photodegradation	**TEST (Estimate)**	**TEST**	**TEST**	**TEST**
7.0 Stability in Water	**TEST (OECD 111)**	**TEST**	**TEST**	**TEST**
8.0 Transport and Distribution	**TEST (Fugacity Model*)**	**TEST**	**TEST**	**TEST**
9.0 Biodegradation	**TEST (OECD 301F)**	Adequate	Testing Not Required	**TEST**
10.0 Acute Toxicity to Fish	**TEST (OECD 203)**	Adequate	Adequate	**TEST**
11.0 Acute Toxicity to Algae	**TEST (OECD 201)**	Adequate	Adequate	**TEST**
12.0 Acute Toxicity to Daphnia	**TEST (OECD 202)**	Adequate	Adequate	**TEST**
13.1 Acute Oral Toxicity	Adequate	Adequate	Adequate	Adequate
13.2 Acute Dermal Toxicity	Adequate	Adequate	Adequate	Adequate
13.3 Acute Inhalation Toxicity	Adequate	Adequate	Adequate	Adequate
14.0 Chromosomal Aberration Assay	Adequate	Adequate	Adequate	Adequate
15.1 Mutagenicity (Ames –*In vitro* Bacterial Test)	Adequate	Adequate	Adequate	Adequate
15.2 Mutagenicity (*In vitro* Mammalian Cell Mutation Assay)	**TEST (OECD 476)**	Testing Not Required	Testing Not Required	**TEST**
16-18 Combined Repeat Dose, Reproductive, and Developmental Toxicity	**TEST (OECD 422)**	Testing Not Required	Testing Not Required	**TEST**

*: EQC Level III Fugacity Model

1: The test methods used for the TDP will be used for all compounds, where a TEST is indicated

→ *Increasing TPP content*